IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICATION NUMBER	:	487,761
PATENT NUMBER	:	6,217,866
FILING DATE	:	June 7, 1995
ISSUE DATE	:	April 17, 2001
INVENTOR(S)	:	Schlessinger, et al.

Commissioner of Patents and
Trademarks
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

Aventis Pharmaceuticals Inc., assignee of U.S. Patent No. 6,217,866 ("the '866 patent"), through its appointed agent, ImClone Systems Incorporated, submits this request for patent term extension for the '866 patent.

1. On February 12, 2004, the U.S. Food and Drug Administration ("FDA") approved the monoclonal antibody ("MAb") ERBITUX™ (cetuximab) for use in combination with irinotecan in the treatment of patients with Epidermal Growth Factor (EGF) Receptor (EGFR)-expressing, metastatic colorectal cancer who are refractory to irinotecan-based chemotherapy.

   ERBITUX MAb is a recombinant, human/mouse chimeric, monoclonal antibody that binds specifically to the extracellular domain of the human EGFR. The MAb ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX MAb is produced in mammalian (murine myeloma) cell culture.

   The MAb ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and water for Injection. A copy of the package insert is attached hereto at Tab A.

2. Regulatory review of the combination therapy involving the ERBITUX MAb and irinotecan occurred under § 351 of the Public Health Service Act.

3. The combination therapy involving ERBITUX MAb and irinotecan received permission on February 12, 2004 for commercial marketing under § 351 of the Public Health Service Act.

4. Neither ERBITUX MAb, nor the approved combination therapy with irinotecan, have been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. This application is submitted by the owner of the patent, Aventis Pharmaceuticals Inc., through its agent, ImClone Systems Incorporated, within the sixty (60) day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day that this application may be submitted is April 12, 2004. The Assignment record for name change from Rhone-Poulenc Rorer Pharmaceuticals Inc. to Aventis Pharmaceuticals Inc. is attached as Tab B. Also, the Appointment of Agent from Aventis Pharmaceuticals Inc. to ImClone Systems Incorporated is attached at Tab C.

6. The patent for which an extension is being sought is U.S. Patent No. 6,217,866, which issued April 17, 2001. The inventors listed on the face of the '866 patent are Joseph Schlessinger, David Givol, Richard Kris, George A. Ricca, Christopher Cheadle, and Victoria J. South. Under 35 U.S.C. § 154(a)(2), the '866 patent expires on April 17, 2018. A terminal disclaimer originally filed in parent Application No. 07/244,737 is being re-filed concurrently with this application and under this terminal disclaimer the '866 patent will expire on January 17, 2017.

7. A copy of the '866 patent is attached hereto at Tab D.

8. A copy of the terminal disclaimer discussed in paragraph 6 is attached hereto at Tab E. A copy of the certificate of correction that was filed on December 11, 2001, is attached hereto at Tab F. No reexamination certificates have been issued. A maintenance fee payment is not due until April 19, 2004. (See attached record of fee due dates at Tab G). Accordingly, no copy of a receipt of maintenance fee payment is available.

9. The '866 patent claims the approved combination therapy. The applicable patent claims and the manner in which each applicable claim reads on the approved product is as follows.

> Claim 1. A method for inhibiting the growth of human tumor cells that express human EGF receptors and are mitogenically stimulated by EGF, the method comprising administering an effective amount of an anti-neoplastic agent and an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells; (i) wherein said antibody binds to the extra-cellular domain of the human EGF receptor of said

tumor cell; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibit the binding of EGF to the EGF receptor.

ERBITUX MAb has been approved for the administration, in combination with an antineoplastic agent, to a human cancer patient having tumor cells that express human EGFR. *See, e.g.*, Package Insert at Indications and Usage. Such administration of the ERBITUX MAb is separately from, and therefore not conjugated to, the antineoplastic agent. The MAb ERBITUX binds specifically to the extra-cellular domain of the human EGFR, (*see, e.g.*, Package Insert at Description), and competitively inhibits the binding of EGFR and other ligands. *See, e.g.*, Package Insert at Clinical Pharmacology. *In vitro* assays and *in vivo* animal studies have shown that binding of the MAb ERBITUX to the EGFR results in inhibition of cell growth. *See, e.g.*, Package Insert at Clinical Pharmacology. Expression of EGFR is confirmed by immunohistochemical analysis of the tumor cells using the DakoCytomation EGFR pharmDx™ test kit. *See, e.g.*, Package Insert at EGFR Expression and Response. Moreover, the approved combination includes the anti-neoplastic agent irinotecan, which belonging to a general group of chemotherapy drugs known as topoisomerase inhibitors that stop the growth of cancer cells by preventing the development of elements necessary for cell division, and is indicated for treatment of colon and rectal cancers.

10. The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period is:

IND number: BB-IND 5804

IND effective date: 11/18/1994

BLA number: STN BL 125084/0

BLA submission date: 8/12/2003

BLA effective date: 8/14/2003

BLA approval date: 2/12/2004

11. The combination therapy of the MAb ERBITUX and irinotecan was approved by the FDA following submission of an IND and a BLA filed by ImClone Systems Incorporated. ImClone Systems Incorporated is the licensee of the '866 patent. As a brief description of the significant activities undertaken by ImClone Systems Incorporated during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities, attached hereto at Tab H is a chronology of the communications with the FDA during the regulatory review period ending with the approval on February 12, 2004. Individual's names and proprietary information has been redacted.

12. In the opinion of the applicant, the '866 patent is eligible for patent term extension under 35 U.S.C. § 156 because:

(a) 35 U.S.C. § 156(a)

The '866 patent claims a method of using a product.

(b) 35 U.S.C. § 156(a)(1)

The term of the '866 patent has not expired before submission of this application under subsection (d)(1).

(c) 35 U.S.C. § 156(a)(2)

The term of the '866 patent has never been extended under subsection (e)(1).

(d) 35 U.S.C. § 156(a)(3)

The application for extension is submitted by Aventis Pharmaceuticals Inc., assignee of the '866 patent, through its appointed agent, ImClone Systems Incorporated, in accordance with the requirement of 35 U.S.C. § 156(d) paragraphs (1)-(4) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4)
ERBITUX MAb has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A)
The commercial marketing or use of the MAb ERBITUX after the regulatory review period is the first permitted commercial marketing or use of the ERBITUX MAb, under the provision of section 351 of the Public Health Service Act under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4)
No patent other than the '866 patent has been extended under subsection (e)(1) for the same regulatory review period for ERBITUX MAb.

The length of extension of the patent term of the '866 patent claimed by applicant is 391 days, until 2/12/2018. The length of the extension was determined as follows.

(a) 3,192 The number of days in the period beginning on the date an exemption under section 351 of the Public Health Service Act became effective for the approved product (11/18/1994) and ending on the date the application was initially submitted and effective for such product under section 351 of the Public Health Service Act. (8/14/03); (See 37 C.F.R. § 1.775(c)(1)).

(b) 183 The number of days in the period beginning on the date the application was initially submitted and effective for the approved product under section 351 of the Public Health Service Act, (8/14/03) and ending on the date such application was approved under such section. (2/12/04). (See 37 C.F.R. § 1.775(c)(2)).

(c) 3,375 The sum of (a) and (b). This is the regulatory review period. (37 C.F.R. § 1.775(c)).

(d) 2,343 The number of days in the regulatory review period which were on and before the '866 patent issued. (April 17, 2001). (37 C.F.R. § 1.775(d)(1)(i)).

(e) 0* The number of days in the regulatory review period during which it is determined under 35 U.S.C. § 56 (d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence. (37 C.F.R. § 1.775(d)(1)(ii)).

* There has been no such determination. To the best of applicant's knowledge, ImClone Systems Incorporated was diligent during the regulatory review period.

(f) 2,343 The sum of (d) and (e).

(g) 1,032 (c)-(f). (37 C.F.R. § 1.775(d)(1)(ii)).

(h) 1,779 ½ of (a) + (b). (37 C.F.R. § 1.775(d)(1)(iii)).

(i) 1/17/2017 The original term of the '866 patent, shortened by any terminal disclaimer.

(j) 12/1/2022 The original term of the patent as shortened by any terminal disclaimer plus the number of days in (h). (37 C.F.R. § 1.775(d)(2)).

(k) 2/12/2018 The date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act plus 14 years. (37 C.F.R. § 1.775 (d)(3)). (2/12/2004)

(l) 2/12/2018 The earlier of (j) and (k). (37 C.F.R. § 1.775(d)(4)).

(m) 1/17/2022 (i) plus 5 years. (37 C.F.R. § 1.775 (d)(5)(i)).

(n) 2/12/2018 The earlier of (l) and (m). (37 C.F.R. § 1.775(d)(5)(ii)).

13. The applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

14. Please charge the prescribed fee for receiving and acting upon this application for patent term extension pursuant to 37 C.F.R. § 1.20(j) to deposit account 11-0600.

15. Please address inquires and correspondence to:

Deborah A. Somerville
KENYON & KENYON
One Broadway
New York, NY 10004

16. A triplicate of these application papers is submitted herewith.

17. The following declaration of Deborah A. Somerville of Kenyon & Kenyon, is submitted herewith in compliance with the requirements of 37 C.F.R. § 1.740(b).

DECLARATION

The undersigned, Attorney for the Applicant's agent, ImClone Systems Incorporated, in compliance with 37 C.F.R. §1.740 (b)(1) (see Tab I for Power of Attorney to Deborah A. Somerville from ImClone Systems Incorporated), hereby declares as follows:

1. I am a patent attorney authorized to practice before the United States Patent and Trademark Office (Reg. No. 31,995) and I am authorized to represent ImClone Systems Incorporated in this application for patent term extension of the 6,217,866 patent and to transact all business in the United States patent and Trademark Office in connection therewith;

2. I have reviewed and understand the contents of this application for patent term extension of U.S. Patent No. 6,217,866 ("the '866 patent");

3. I believe that the '866 patent is subject to patent term extension pursuant to provisions of 37 C.F.R. § 1.710;

4. I believe that the extension of the length claimed in this application for patent term extension of the '866 patent is justified under 35 U.S.C § 156 and the applicable regulations relating thereto; and

5. I believe that the '866 patent, which is the subject of this application for patent term extension, meets the conditions for patent term extension as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

Dated: 4/8/04

Deborah Somerville/TAL
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Attorney for Applicant's Agent
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